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REMARKS

Claims 44-48 were pending. Claims 44 and 48 have been amended hereinabove. Accordingly claims 44-48 are presently pending.

Support for the amendments in claims 44 and 48 may be found as follows.

New claim 44 is supported in originally filed claim 43 and the specification at page 13, lines 1-4, line 5-7, and lines 33-36; page 14, lines 1-6 and lines 8-18; page 23, lines 26-34.

New claim 48 is supported in the specification at page 23, lines 17-19; page 12, lines 11-17.

Changes in the claims are clearly supported by the specification as originally filed and do not involve new matter. Accordingly, applicants respectfully request entry of them.

Paragraph 2

At paragraph 2b, page 3 of the Office Action, the Examiner is requesting that Applicants indicate whether the application 08/814,279 is a CIP, divisional, or a continuation. Applicants wish to point out to the Examiner that applications 08/814,279, 60/071,141, and 60/074,675 are all provisional applications.

DRAWINGS

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Paragraph 3

At paragraph 3, page 4, of the Office Action, the Examiner is requesting submission of formal drawings. Applicants will attend to this matter.

At paragraph 3b, page 5, of the Office Action, the Examiner states that Figures 4 and 5 are illegible for examination purposes. As stated above, applicants will submit formal drawings.

At paragraph 3c, page 5, of the Office Action, the Examiner requests that Applicants separately label the Figures. Applicants wish to point out to the Examiner that many of the Figures are labeled at the top of the page, and that the labels may be hidden by the clasp at the top of the page.

SEQUENCE LISTING

Paragraph 4

At paragraph 4, page 5, of the Office Action, the Examiner is requiring a corrected Sequence Listing which applicants provide herewith.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Paragraphs 5-6

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The Examiner rejected claims 15, 16, and 21 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim a subject matter which Applicants regard as the invention.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Paragraphs 7-8

The Examiner rejected claims 44-48 under 35 U.S.C. § 112, first paragraph. Allegedly, the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; and (2) reproducible from the written description.

In response to the Examiner's statement that there is insufficient assurances that all required deposits have been made, Applicants respectfully point out that the claimed invention is directed to methods of inhibiting the growth of prostate tumor cells expressing PSCA using antibodies generated from specific hybridomas. Accordingly, Applicants contend that the deposit of these hybridomas teaches a person having ordinary skill in the art to which the subject pertains how to make and use the claimed invention in accordance with 35 U.S.C. § 112.

Moreover, Applicants maintain that the hybridomas (American Type Culture Collection (ATCC), Accession Nos. HB-12612, HB-12616, HB12614, HB12618, or HB-12617) have been deposited pursuant to the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure with the Patent Culture Depository of the ATCC, 10801 University Blvd., Manassas, Virginia 20110-2209 U.S.A.

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Applicants maintain that during the pendency of the subject application, access to the ATCC deposits will be afforded to one determined by the Commissioner to be entitled thereto under 35 U.S.C. §1.14 and §122, and all restrictions on the availability to the public of the material deposited under ATCC Accession Nos. HB-12612, HB-12616, HB12614, HB12618, or HB-12617 will be irrevocably removed upon the issuance of a patent from the subject application.

Furthermore, the above deposits will be maintained by the ATCC for a period of 30 years from the date of deposit or at least 5 years after the last request for a sample of the deposited material, whichever is longer. Where the ATCC cannot furnish samples of the above deposits for any reason, Applicants shall make a replacement deposit, of the material which was originally deposited, within three months of receiving notification that the ATCC cannot furnish samples. All restrictions on the availability to the public of the deposited cell lines will be irrevocably removed upon the granting of a patent of the subject application.

Paragraph 9

The Examiner rejected claims 44-48 under 35 U.S.C. § 112, first paragraph for reasons of record. Briefly stated, the issue is whether the field of antibody therapy is unpredictable and, consequently, the presently claimed invention is not enabled by the disclosure.

Applicants respectfully traverse the rejection.

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THE LEGAL STANDARD

The legal standard for enablement requires that there must be sufficient disclosure through illustrative examples or terminology to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.¹ This means that the disclosure "must adequately guide the art worker to determine, without undue experimentation, which species among the claimed genus possess the disclosed utility."² As discussed *supra* with respect to the specification's disclosed methods, by providing illustrative examples and assays, Applicants have met the standard for objective enablement.³

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all factual considerations⁴ (MPEP § 2164.08, §2164.05(a), §2164.05(b), §2164.03, §2164.02, and 2164.06). As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

¹ *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991).

² *Id.*

³ The first paragraph of § 112 requires nothing more than objective enablement. *In re Marzocchi*, 439 F.2d 220, 223 (CCPA 1971). How such a teaching is set forth, either by the use of illustrative examples or by broad terminology is irrelevant. *Id.*

⁴ *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404

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Paragraphs 9a-e

The Claimed Method is Predictable

The Office maintains the rejection under 35 U.S.C. § 112 for lack of enablement based on its assertion that antibody immunotherapy must be predictable in order for the invention to also be considered reliable. Applicants strongly disagree that the enablement of the invention is reliant upon the success of the general field of antibody immunotherapy.

According to MPEP §2164.04, “[b]efore any analysis of enablement can occur, it is necessary for the Examiner to construe the claims.” Applicants are claiming methods for inhibiting the growth of prostate tumor cells expressing PSCA comprising administering to a patient a monoclonal antibody designated ATCC No. HB-12612, ATCC No. HB-12616, ATCC No. HB12618, or ATCC No. HB-12617 which binds specifically to the extracellular domain of PSCA in an amount effective to inhibit growth of the prostate tumor cells. Applicants contend that it is the predictability of this claimed method that is the appropriate concern for the Office and not the broad field of antibody immunotherapy.

It is well settled that the Patent Office has the initial burden of presenting evidence as to why it doubts the truth or accuracy of any statement in a supporting disclosure. Otherwise there would be no need for the Applicant to go to the trouble of supporting his presumptively accurate disclosure. In re Marzocchi, 439, F.2d 220, at 224, 169 U.S.P.Q. 367, at 370 (CCPA 1971), cited in MPEP §2164.04. Here, the Office relies on excerpts from three references to support its conclusion that antibody immunotherapy is not predictable.

However, in the context of the articles in which the quotations appear, these excerpts do not suggest a lack of predictability of the claimed invention. As a matter of fact, these references

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suggest the opposite.

Jain et al.

The Office states that Jain discloses the art known barriers to the delivery of drugs into solid tumors. Impediments to drug delivery include (1) nonuniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all; (2) increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor; (3) high liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agent, such as antibodies, into tumors; (4) convection is a necessary mechanism by which larger therapeutic molecules such as antibodies, reach target cells which are not directly fed by the vasculature; (5) molecules as large as antibodies would require several months to reach a uniform concentration in a tumor that measures 1 cm. in radius.

Jain does not undermine antibody immunotherapy. In fact, Jain is not a review article on antibody therapy; but, instead, discusses the physical aspects of the tumor (e.g., barriers to drug penetration) that may make a tumor resistant to anticancer agents.

Jain is concerned with optimization of drug delivery in connection with tumor killing and never states that antibody therapy (or any other type of drug therapy) is inoperable. Jain merely discloses that more work has to be done in connection with factors that govern blood flow and the movement of molecules and cells within tumors in order to optimize existing tumor therapy of every kind (Jain at page 65, left column, second full paragraph).

Moreover, Jain discloses that the impediments as described by the Examiner above can be beneficial (Jain at page 64, left column, first full paragraph). For example, "some big molecules would still enter the matrix" (Jain at page 61, middle column, first paragraph); once in the core of

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the tumor, large molecules that are "sticky" may be of benefit because the "stickiness can help retain a drug in a tumor" (Jain at page 64, left column, second paragraph). Further, Jain also gives one example of how antibody therapy may work (Jain at page 64, right column, first full paragraph).

For the reasons discussed above, applicants respectfully contend that Jain does not imply that the success of the present invention is unpredictable.

Chatterjee et al.

The Office contends that Chatterjee et al. teaches that for any novel therapy the transition from the laboratory to the clinic is a quantum leap.

Chatterjee does not undermine antibody immunotherapy. Nowhere does Chatterjee state that Ab therapy is inoperable. Chatterjee is merely a review article on the use of anti-idiotype (anti-Id) antibody therapies. Like Jain, Chatterjee is concerned with optimization of drug delivery in connection with tumor killing.

Chatterjee discusses current anti-Id therapy experiments, e.g., pre-clinical studies with anti-idiotype targeting the carcinoembryonic antigen (CEA); pre-clinical studies with anti-idiotype targeting melanoma-associated proteoglycan antigen; pre-clinical studies with anti-idiotype targeting human breast tumor-associated antigen; phase I clinical trials of colorectal cancer, melanoma and B cell lymphoma patients. Antibody therapy was successful in almost all of the preclinical and clinical trials discussed (Chatterjee at pages 76-78).

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For example, Chatterjee teaches that since the immune response has a limited capacity, immunotherapeutic manipulations to destroy a tumor will probably be most effective against small tumor masses (Chatterjee at page 81, left column, last paragraph). Chatterjee teaches that immunotherapy with anti-idiotype antibodies should prove most curative in the adjuvant setting where the disease has been controlled or stabilized with conventional therapies. Also, anti-Id in combination with tumor vaccines is postulated to be an attractive alternative (supra).

As a further affirmation of antibody therapy, Chatterjee discloses the operability of the use of soluble anti-Id mAbs as immunostimulators in tumor-bearing mice (Chatterjee at page 76, right column, second full paragraph). Although this treatment did not induce cures, it significantly increased survival time (supra). These results provide guidelines for developing clinical protocols for cancer patients by using combination therapy of anti-Id and chemotherapy (supra).

The Examiner doubts the success of the invention because of numerous listed considerations in the prior art. As discussed above, these considerations are speculative and are not evidence of unpredictability of the claimed methods. The concerns of the art go more towards the question of optimizing the antibody therapy than demonstrating that antibody therapy is not predictable.

Additionally, the Office questions the teaching of the present application, with respect to dosages, the route, time course and administration means (Office Action at page 11, paragraph 9c). It is well known in the art that the most effective mode of administration and dosage regimen for the molecules of the present invention depends upon the exact location of the prostate tumor being treated, the severity and course of the cancer, the subject's health and response to treatment and the judgment of the treating physician. Accordingly, it would be within the skill of those in the art to modify the dosages of the molecules to the individual subject. Similarly, the route and time course of administration and sites can be optimized without undue experimentation.

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Moreover, it is understood and accepted in the field that certain parameters for treatment may require additional efforts towards developing a commercially successful therapeutic end product. The considerations listed by the Examiner are refinements that one skilled in the art would determine for commercialization.

In general, there is much evidence to indicate that antibody immunotherapy, routinely used in the art, is a predictable technology. The Patent and Trademark Office has previously recognized the predictability of antibody immunotherapy. Surely a technology with so much support is not unpredictable.

Paragraph 9f

The Office alleges that the specification does not disclose whether the method is effective in animals with preexisting tumor and this is a significant omission in view of the well known immunosuppressive effects of certain tumor. Allegedly, the criticality of a working example encompassing all of the methods steps, especially the treatment of pre-existing neoplasia, is underscored by Gura et al.

Applicants are not required, under 35 U. S. C. §112, to disclose whether the claimed methods are effective in animals with preexisting tumors. Applicants are required to show how to make and use the claimed methods without undue experimentation.

In this regard, the specification provides a description of the claimed methods. For example, applicants teach how to make and use methods for selectively killing a cell expressing PSCA comprising reacting a monoclonal antibody designated 1G8 (ATCC No. HB-12612), 3C5 (ATCC No. HB-12616), 3E6 (ATCC No. HB12618), , or 4A10 (ATCC No. HB-12617) conjugated to a therapeutic agent with the cell so that the therapeutic agent conjugated to the antibody can kill the

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cell (specification at page 10, lines 9-10, 13-15, 29-30; page 4, lines 1-5; page 9, lines 32-35; Figures 7, 9, 10, 11, 13 and generally throughout the specification).

Further, applicants teach how to make and use methods of inhibiting the growth of prostate tumor cells expressing PSCA comprising administering to a patient a monoclonal antibody designated ATCC No. HB-12612, ATCC No. HB-12616, ATCC No. HB12618, or ATCC No. HB-12617 which binds specifically to the extracellular domain of PSCA in an amount effective to inhibit growth of the prostate tumor cells (specification at page 9, lines 32-35; page 10, lines 9-10, 13-15, 29-30; page 11, lines 15-16; page 13, lines 33-36; page 14, lines 1-19; page 23, lines 29-35; and pages 24-25; and generally throughout the specification).

As post filing confirmatory support of applicants' assertion, applicants provide the following data.

FIG. 48. Demonstrates complete inhibition of LAPC-9 prostate tumor growth in SCID mice by treatment with anti-PSCA monoclonal antibodies. The upper panel represents mice injected with LAPC-9 s.c. and treated with a mouse IgG control, while in the lower panel mice were injected with LAPC-9 s.c. but treated with the anti-PSCA mAb cocktail. Each data point represents the ellipsoidal volume of tumors at specified time points as described in Example 18-A. In the anti-PSCA group, an arbitrary value of 20 was given for all data points to create a line, although the actual tumor volume was 0 (Example 18-A).

FIG. 49. Shows the characteristics of anti-PSCA monoclonal antibodies utilized in the in vivo tumor challenge study described in Example 18. (A) Isotype and epitope map: The region of PSCA protein recognized by the anti-PSCA mAbs was determined by ELISA analysis using GST-fusion proteins (50ng/well) encoding the indicated amino acids of PSCA. Following

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incubation of wells with hybridoma supernatants, anti-mouse-HRP conjugate antibody was added and reactivity was determined by the addition of 3,3' 5,5'- Tetramethylbenzidine base (TMB) substrate. Optical densities (450nm) are the means of duplicate determinations. (B) Epitope map determined by Western analysis: 50ng of the indicated GST-PSCA fusion protein was separated by SDS-PAGE and transferred to nitrocellulose. Western analysis was carried out by incubation of blots with hybridoma supernatants followed by anti-mouse-HRP secondary Ab and visualized by enhanced chemiluminescence.

FIG. 53. Demonstrates inhibition of LAPC-9 tumor growth by anti-PSCA monoclonal antibodies. The top panel represents mice injected with 1×10^6 LAPC-9 s.c. and treated with a mouse IgG control ($n = 10$), the middle panel represents mice injected with LAPC-9 s.c. and treated with anti-PSCA mAb cocktail ($n = 10$), the bottom panel represents mice injected with LAPC-9 s.c. and treated with bovine IgG ($n = 5$). Each data point represents the ellipsoidal volume of tumors at specified time points as described in Example 18-B.

FIG. 54. Demonstrates inhibition of LAPC-9 tumor growth by the anti-PSCA monoclonal antibody 1G8. The upper panel represents mice injected with 1×10^6 LAPC-9 s.c. and treated with a mouse IgG control ($n = 6$), while in the lower panel mice were injected with LAPC-9 s.c. but treated with the anti-PSCA mAb 1G8 ($n = 7$). Each data point represents the ellipsoidal volume of tumors at specified time points.

FIG. 55. Demonstrates inhibition of LAPC-9 tumor growth by anti-PSCA monoclonal antibodies 2A2 and 2H9. The upper panel represents mice injected with 1×10^6 LAPC-9 s.c. and treated with either a mouse IgG control ($n = 6$) or the 2A2 mAb ($n = 7$). The lower panel represents mice injected with LAPC-9 s.c. and treated with the same mouse IgG control ($n = 6$)

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or the 2H9 mAb ($n = 7$). All data points represent the mean ellipsoidal volume of tumors (mm^3) at the specified time points. Error bars represent standard error of the mean (SEM).

FIG. 57. Demonstrates inhibition of established LAPC-9 prostate cancer xenografts by PSCA monoclonal antibody 3C5. See Example 18-C4 for details.

FIG. 65. Shows PSCA Mabs exert growth inhibitory effect through PSCA protein. The growth inhibitory effect of PSCA Mab 1G8 on LAPC-9 and PC-3 prostate tumors is compared, showing no effect on PC-3 tumors, which do not express PSCA antigen, but significant growth inhibition in LAPC-9 tumors, which do express PSCA antigen. See Examples 18-C1, -C3 for details.

FIG. 66. Demonstrates growth inhibition of LAPC-9 (AD) orthotopic tumors by the anti-PSCA MAb 1G8. (A) Mice having moderate levels of serum PSA. Two mg of 1G8 was administered to these mice on days 10, 13, and 15, followed by one mg on days 17, 20, 22, 25, 27, 29, 34, 41, and 49 as indicated by the arrows. (B) Mice having low levels of serum PSA levels. One mg of 1G8 was administered on days 12, 13, 14, 19, 20, 22, 25, 27, 29, and 33 as indicated by the arrows.

FIG. 67. Demonstrates that treatment with the anti-PSCA Mab, 1G8, increases survival of mice bearing LAPC-9 (AD) orthotopic tumors. (A) The mice in Figure 66 A, which were treated with 1G8, exhibited an increase in survival compared to mice treated with PBS. (B) The mice in Figure 66 B, which were treated with 1G8, exhibited an increase in survival compared to mice treated with PBS. There were 4 mice in the PBS-treated group and 5 mice in the 1G8-treated group.

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FIG. 68. Demonstrates growth inhibition of LAPC-9 AD orthotopic tumors by the anti-PSCA MAb 3C5. (A) Mice having moderate levels of serum PSA. One mg of 3C5 was administered on days 6, 8, 10, 13, 15, 17, 20, 22, 24, and 29 as indicated by the arrows. The mice were bled on the days indicated on the X-axis for PSA determinations. (B) Mice having low levels of serum PSA. Two mg of 3C5 was administered on days 9, 12, and 15, followed by one mg on days 18, 20, 22, 25, 27, and 29 as indicated by the arrows. The mice were bled on the days indicated on the X-axis for PSA determinations.

FIG. 69. Demonstrates that treatment with the anti-PSCA Mab, 3C5, increases survival of mice bearing LAPC-9 AD orthotopic tumors. (A) The mice in Figure 68 A, which were treated with 3C5, exhibited an increase in survival compared to mice treated with PBS. There were 4 mice in the PBS-treated group and 5 mice in the 3C5-treated group. (B) The mice in Figure 68 B, which were treated with 3C5, exhibited an increase in survival compared to mice treated with PBS. There were 6 mice in both the PBS-treated and 3C5-treated groups.

FIG. 70. Demonstrates growth inhibition of established PC3-PSCA tumors by 1G8 alone or in combination with doxorubicin. One mg of 1G8 was administered on days 9, 11, 14, 16, 18, 21, 23, 25, and 28 as indicated by the arrows. Doxorubicin (1 mg/kg) was administered on days 9, 16, and 23 as indicated by the (●) symbol.

In view of the specification and the above remarks, applicants have taught how to make and use the claimed methods in accordance with 35 USC §112, first paragraph.

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Gura et al.

Gura does not undermine the predictability of antibody immunotherapy. Gura addresses the issue of optimization of cancer drugs in connection with clinical success. Gura does not discuss antibody immunotherapy. Gura describes systems for identifying and screening cancer drugs, including xenograph models, testing drugs in different cell lines, and knock-out mouse models.

Paragraph 9g

The Examiner states that Seaver supports the unpredictability of selecting which antibody to use as an immunotherapeutic agent. The use of an antibody as an immunotherapeutic agent having a desired specificity and affinity is necessary. The Examiner contends that the present specification is silent concerning the specificity and affinity necessary for the antibodies of the claimed immunotoxin so that one skilled in the art would not be able to practice the claimed invention without undue experimentation:

Applicants respectfully disagree.

The claimed methods are limited to the use of the specified antibodies. There is no reason to believe they would not work as claimed. Further, applicants have demonstrated that the claimed antibodies work as claimed (see Applicants' post filing confirmatory data).

Seaver

Seaver does not undermine antibody immunotherapy. Seaver merely describes the history of antibodies and points out their milestones: e.g., monoclonal antibodies were first generated in

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1976, and single-chain antibodies and humanized antibodies were later made. According to Seaver “[T]he most important factor in determining an antibody’s success as a diagnostic or therapeutic reagent is its specificity.” Seaver goes on to describe the difficulties of finding “good” antibodies and makes a distinction between making a good diagnostic antibody (hard to make) versus making a good therapeutic antibody (at least ten times harder to make). Seaver cites antibodies in current use “antibodies have been administered to prevent hepatitis A and Rh complications during pregnancy” (first page, last column, 3rd paragraph from bottom).

Paragraphs 9h-i

The Examiner states that the specification does not provide working examples wherein all the steps required to practice the claimed methods are employed. The Examiner asserts that lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment *in vivo* of prostate cancer.

Applicants respectfully disagree.

The requirements of 35 U.S.C. §112, first paragraph are fulfilled where one skilled in the art could use the invention given the specification disclosure without undue experimentation³. Undue breadth is analyzed in terms of whether it would have involved undue experimentation to achieve the claimed invention. The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art⁴.

³ In Re Eynde, 480 F2d 1364, 178 USPQ 470 (CCPA 1970).

⁴ Ex parte Forman, et al. 230 USPQ 546, 547 (BPAI 1986).

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The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed⁵.

In Ex parte Forman the Board set forth the following criteria for undue experimentation:

The question of undue breadth is analyzed in the view of:

- (1) the quantity of experimentation necessary,
- (2) the amount of direction or guidance presented,
- (3) the presence or absence of working examples,
- (4) the nature of the invention,
- (5) the state of the prior art,
- (6) the relative skill of those in that art, and
- (7) the unpredictability of the art⁶.

The unpredictability of the art is only one factor that must be evaluated and weighed with the other factors.

In the case of the present invention no undue experimentation would be required to make and use the invention as claimed. The claims are directed to inhibiting the growth of prostate tumor cells expressing PSCA by administering to a patient a monoclonal antibody designated ATCC No. HB-12612, ATCC No. HB-12616, ATCC No. HB12618, or ATCC No. HB-12617 which binds

⁵ Ex parte Forman, et al. 230 USPQ 546, 547 (BPAI 1986).

⁶ Forman at page 547, supra.

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specifically to the extracellular domain of PSCA so as to inhibit the growth of the prostate tumor cells.

The amount of experimentation is minimal because applicants have conducted the relevant experiments which are disclosed in the present application. Ample guidance is presented by applicants as to how to make the antibodies and how to carry out the claimed methods (specification at page specification at page 4, lines 1-5; page 9, lines 32-35; page 10, lines 9-10, 13-15, 29-30; page 11, lines 15-16; page 13, lines 33-36; page 14, lines 1-19; page 23, lines 29-35; and pages 24-25; Figures 7, 9, 10, 11, 13 and generally throughout the specification). The nature of the invention is clear from the disclosure.

The state of the prior art is such that making the antibodies of the invention and introducing such antibodies to contact prostate cancer cells and inhibiting the prostate cancer cells so contacted could be carried out by one skilled in the art with Applicants' disclosure. The relative skill of the art is high, and use of the antibodies of the invention to inhibit cells to which they bind is not unpredictable.

Paragraph 10

Claims 44-48 are granted priority of the March 10, 1998 filing date.

Paragraph 11

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Applicants are pleased that the Examiner has taken the position that claims 44-48 are free of the prior art.

For the reasons discussed above the case has been placed in condition for allowance. Applicants request that the Examiner reconsider and withdraw the outstanding rejections in connection with this case.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 50-0306.

Respectfully submitted,

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FIG. 48

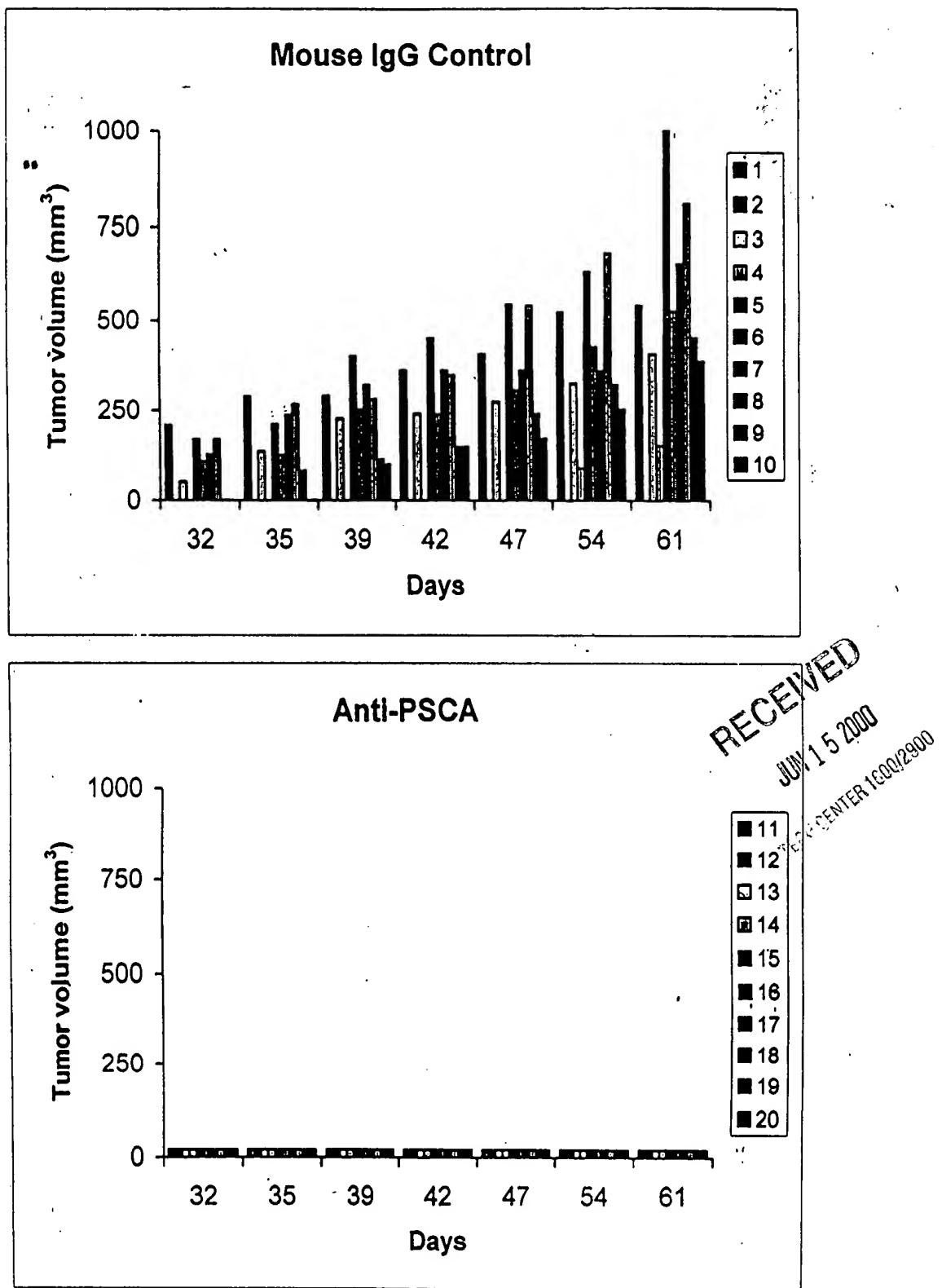


FIG. 53

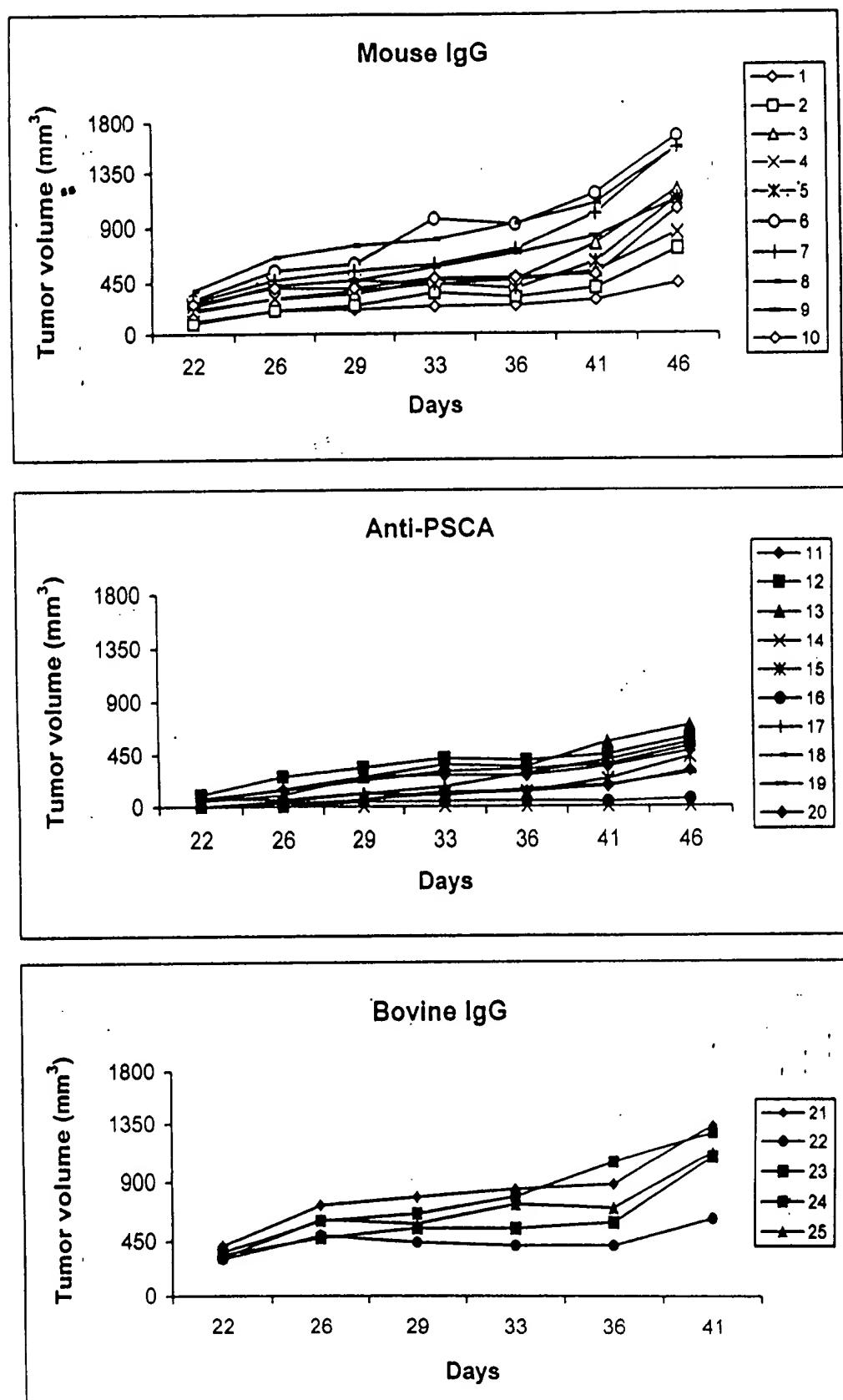


FIG. 54

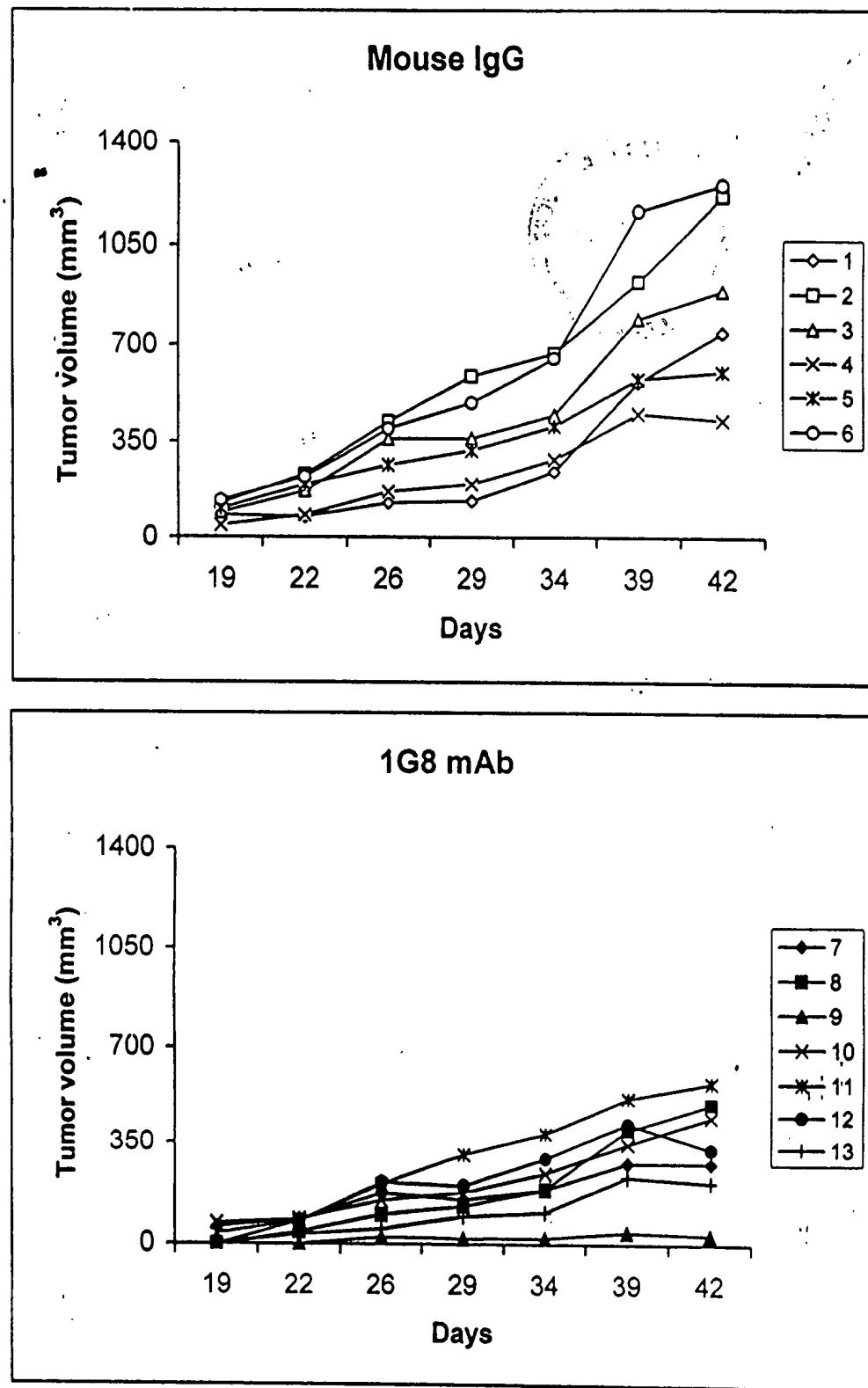


FIG. 55

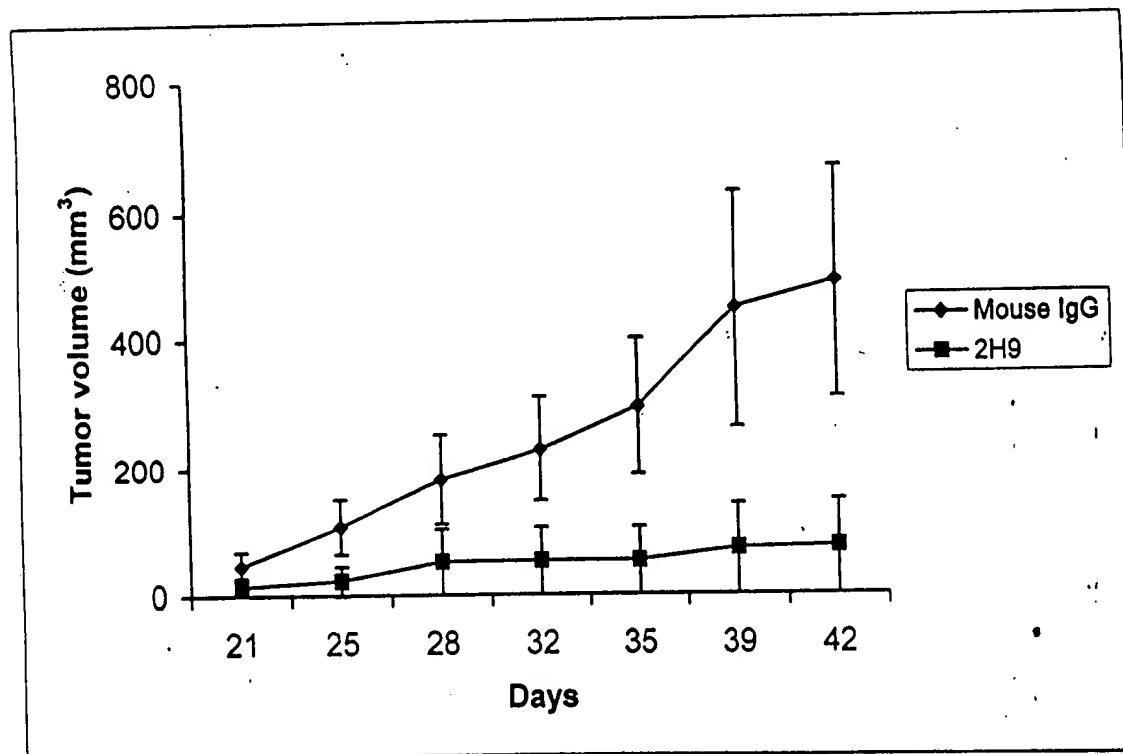
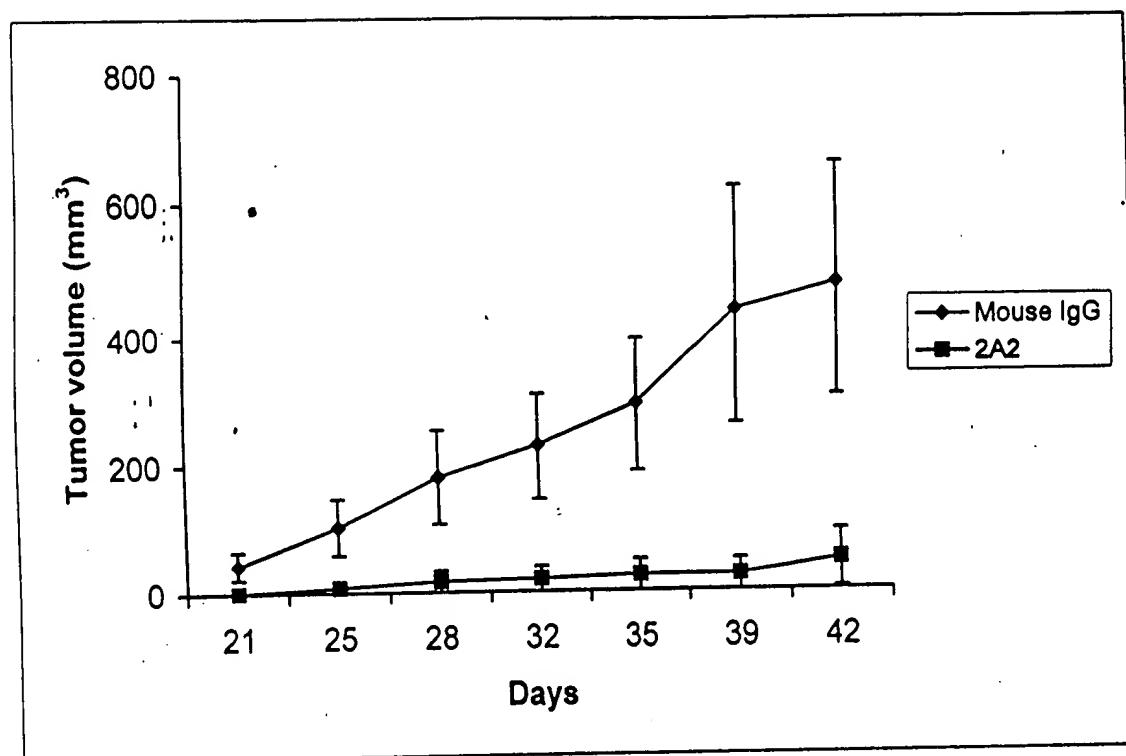
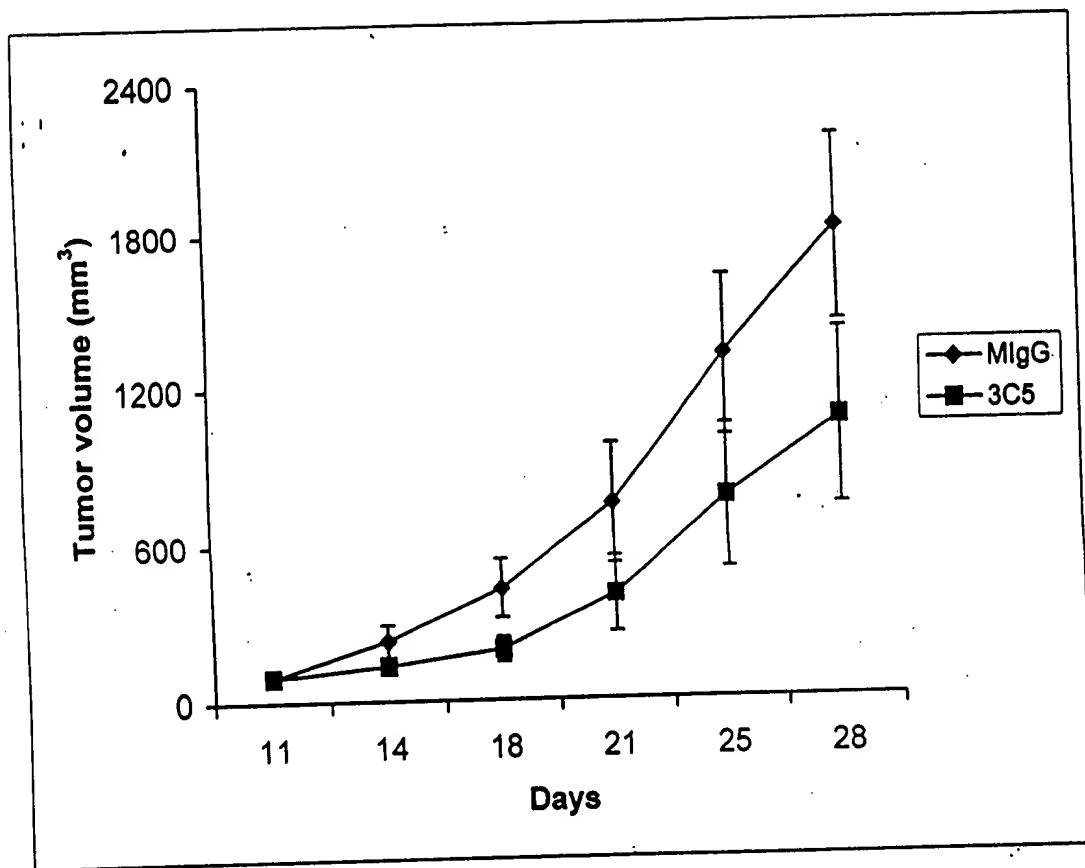


FIG. 57



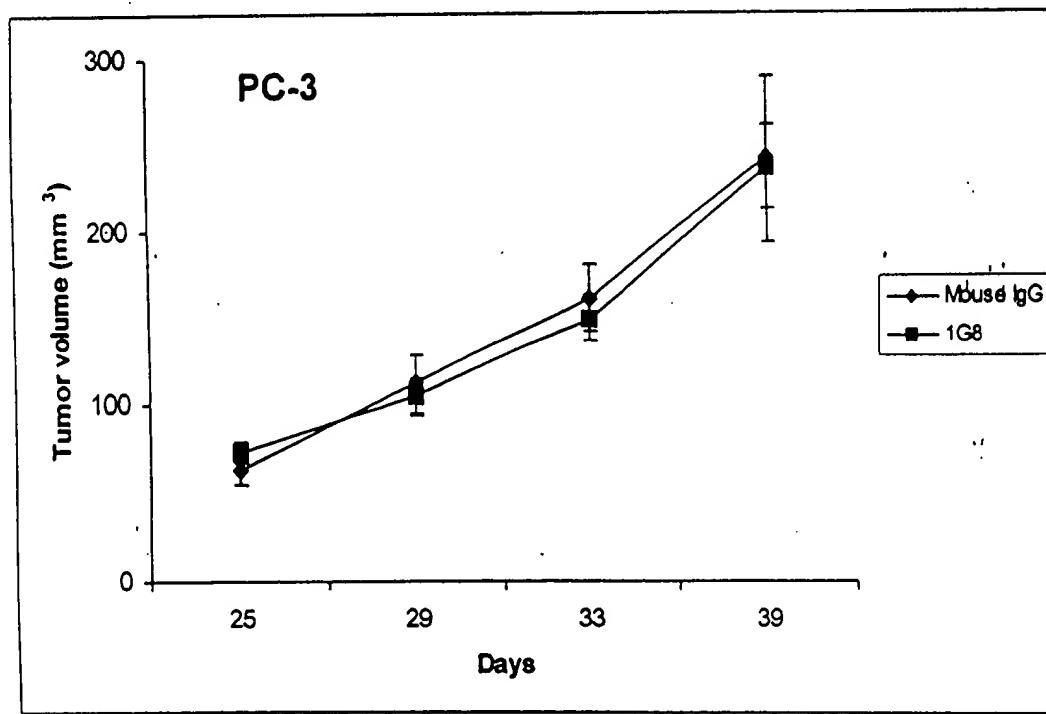
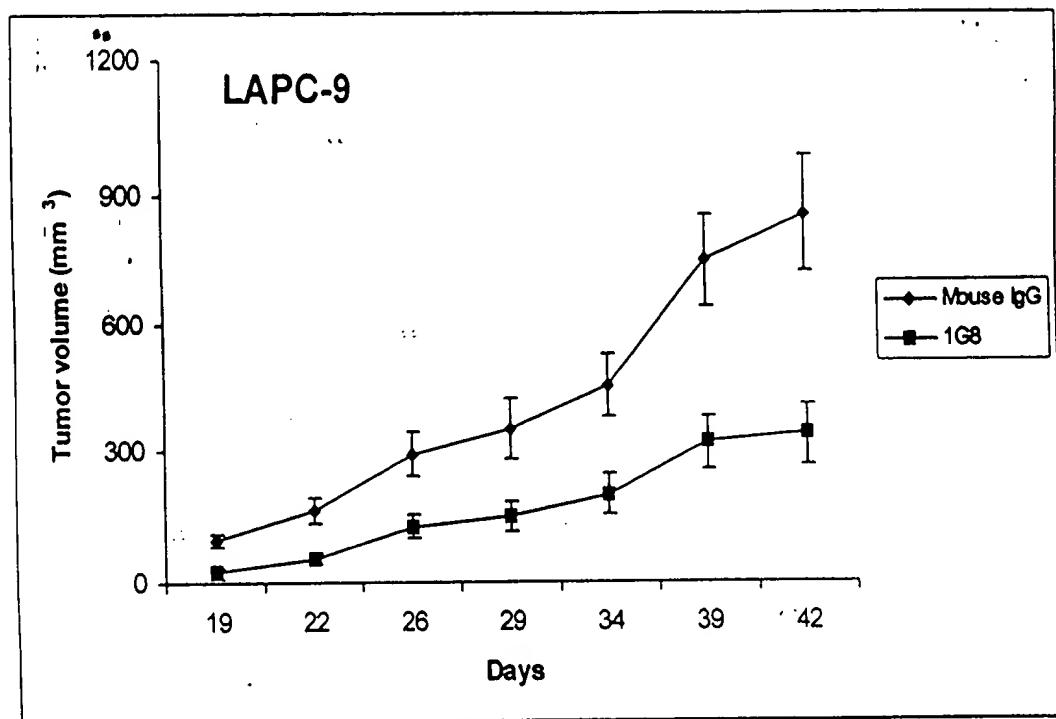
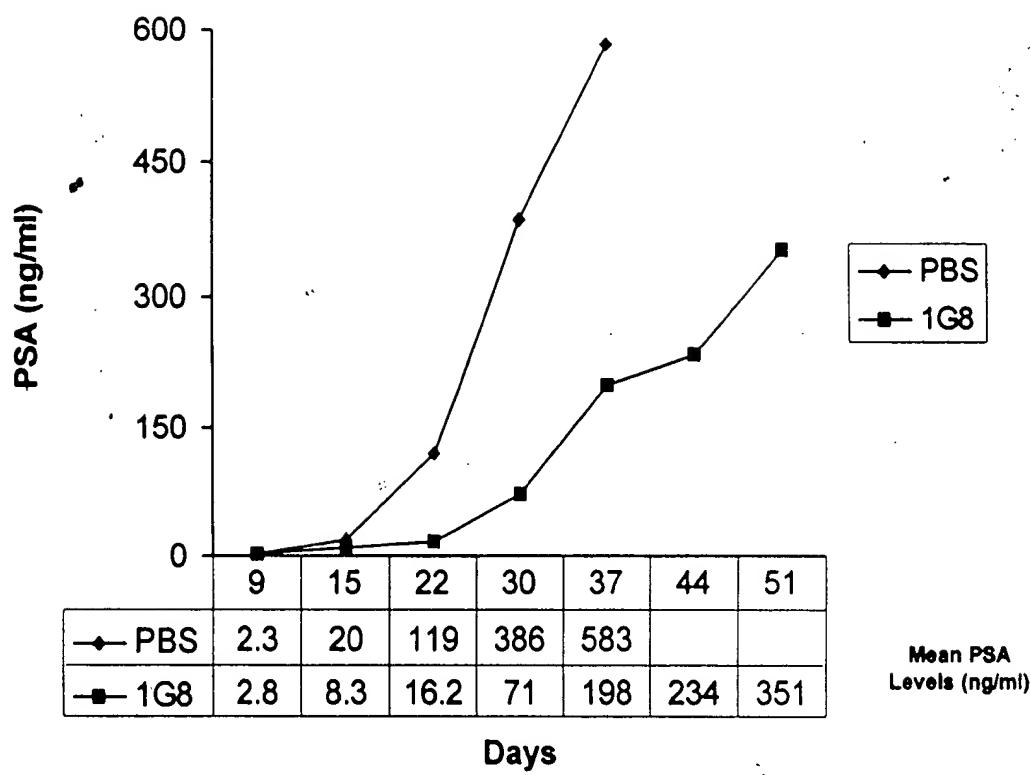


FIGURE 65

A)



B)

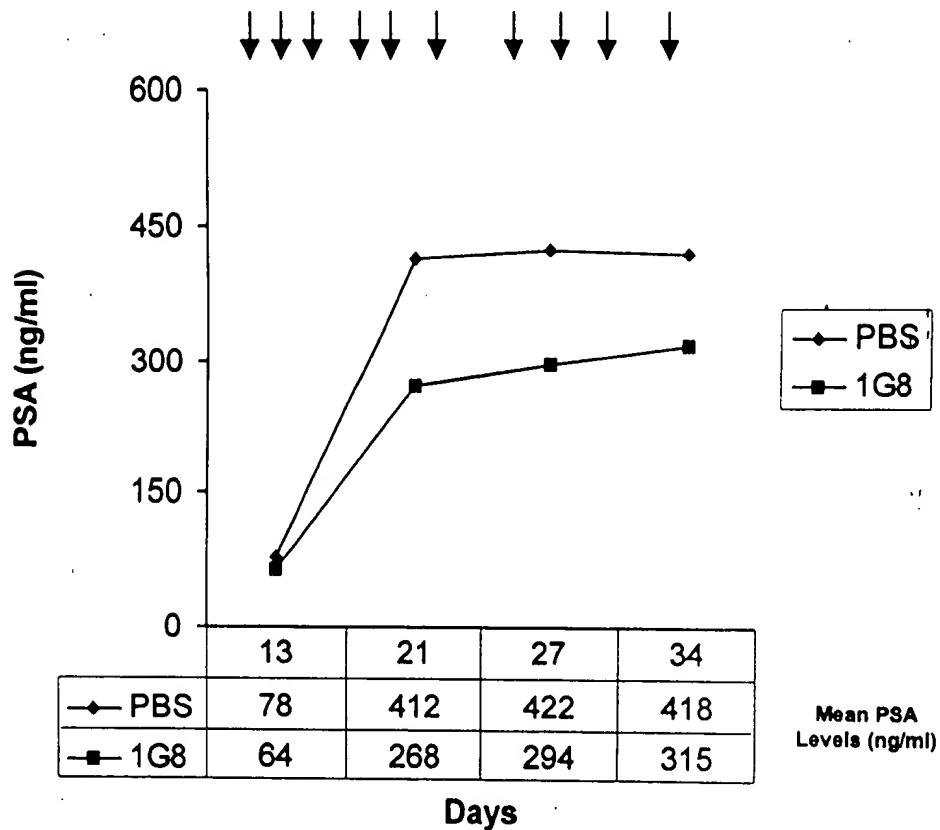


Figure 66

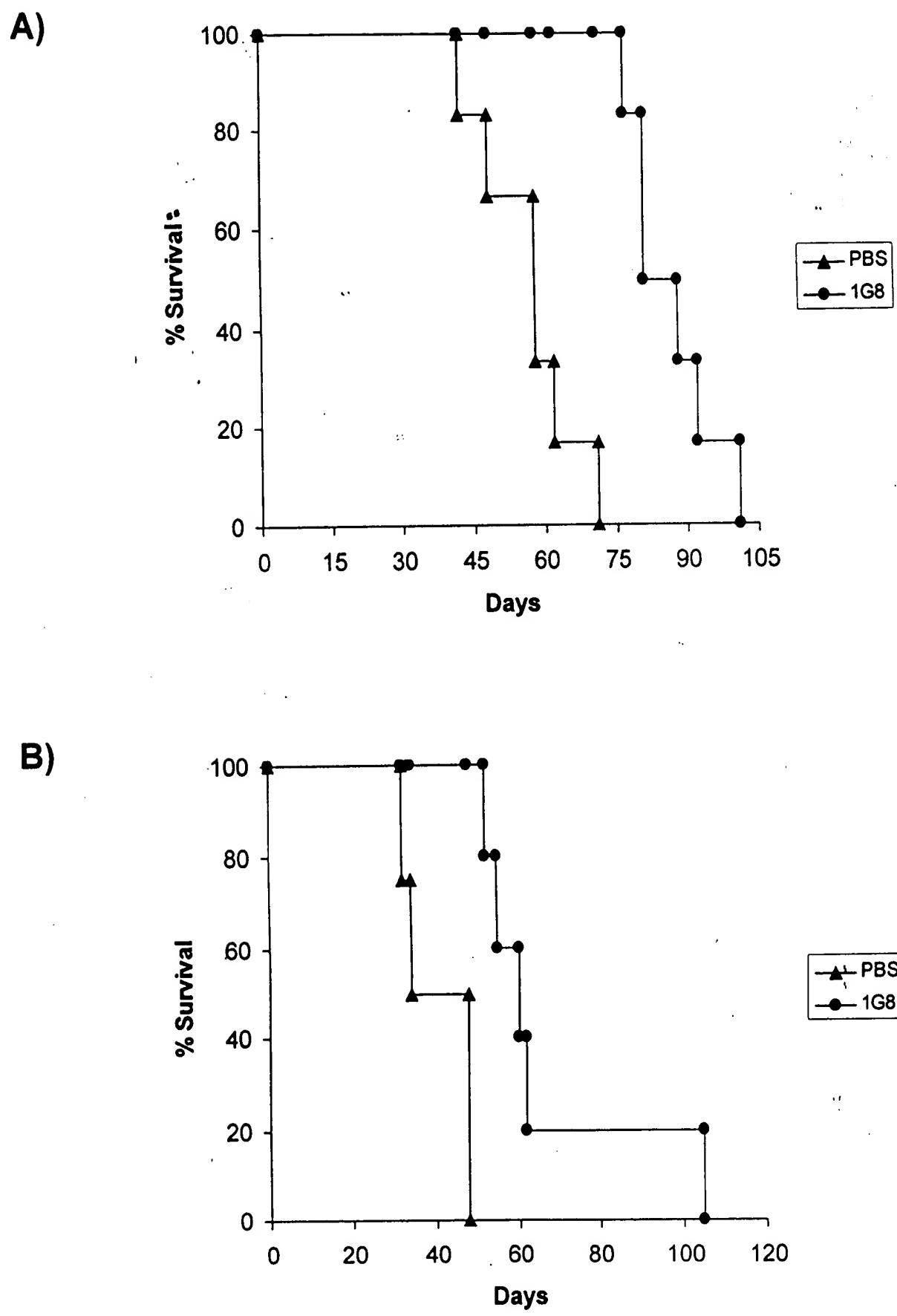
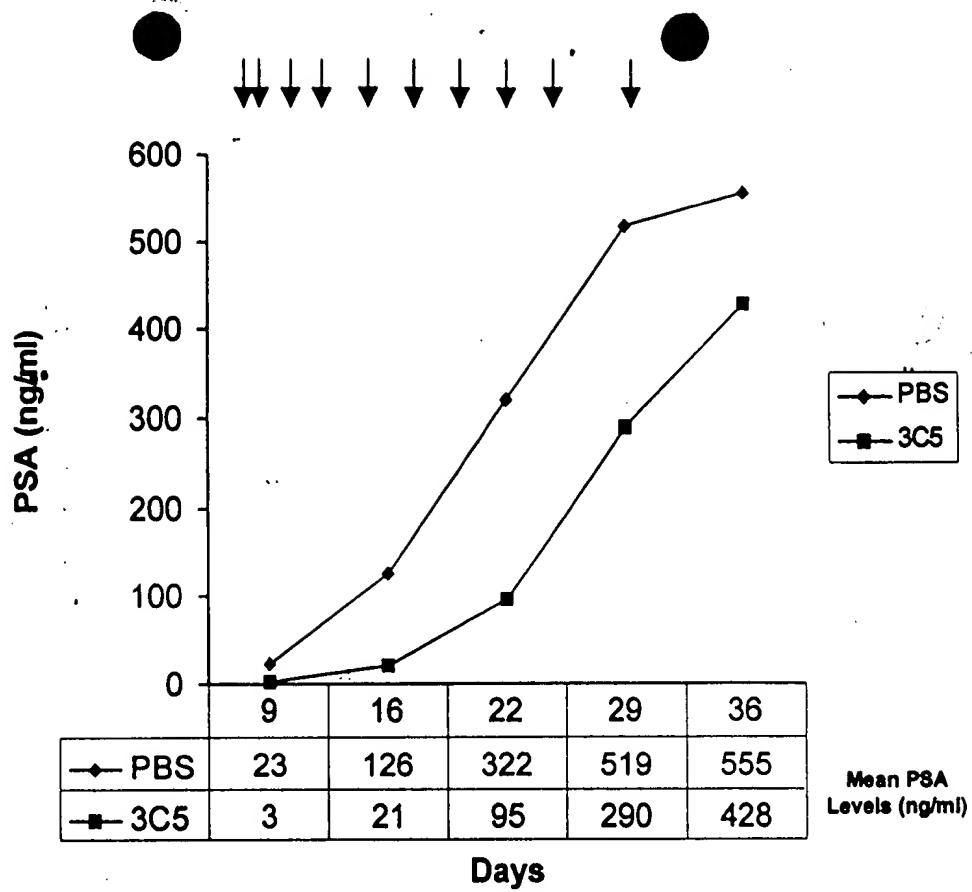


Figure 67

A)



B)

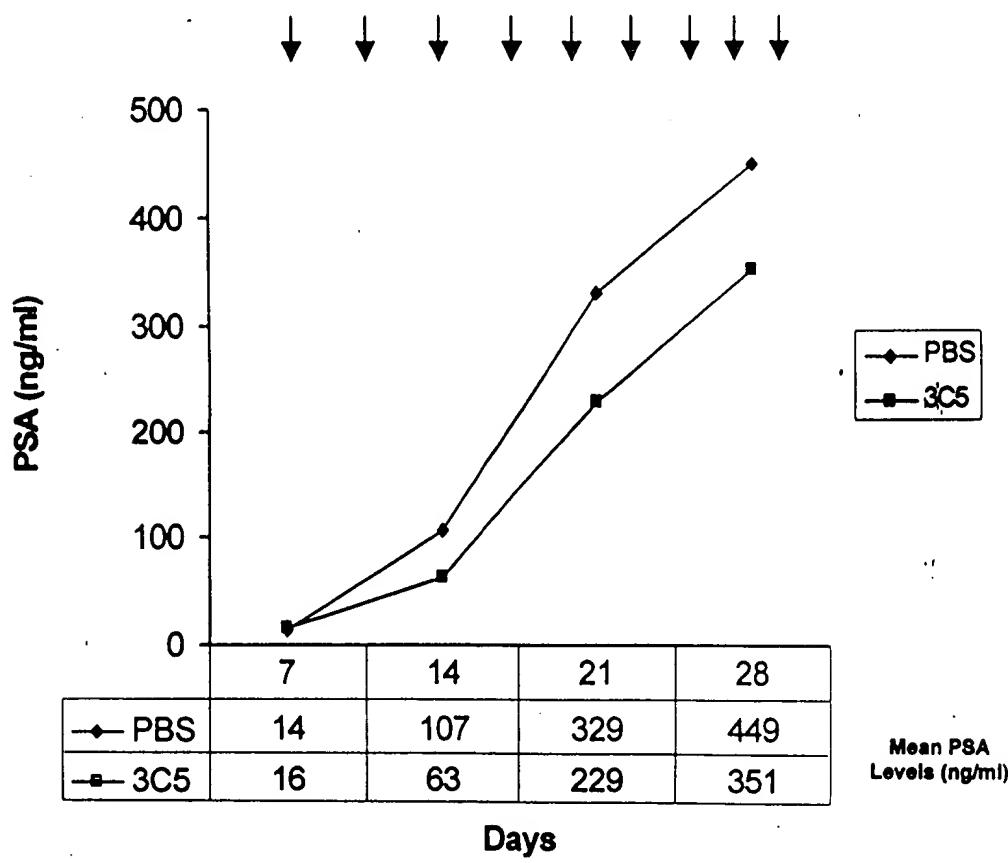
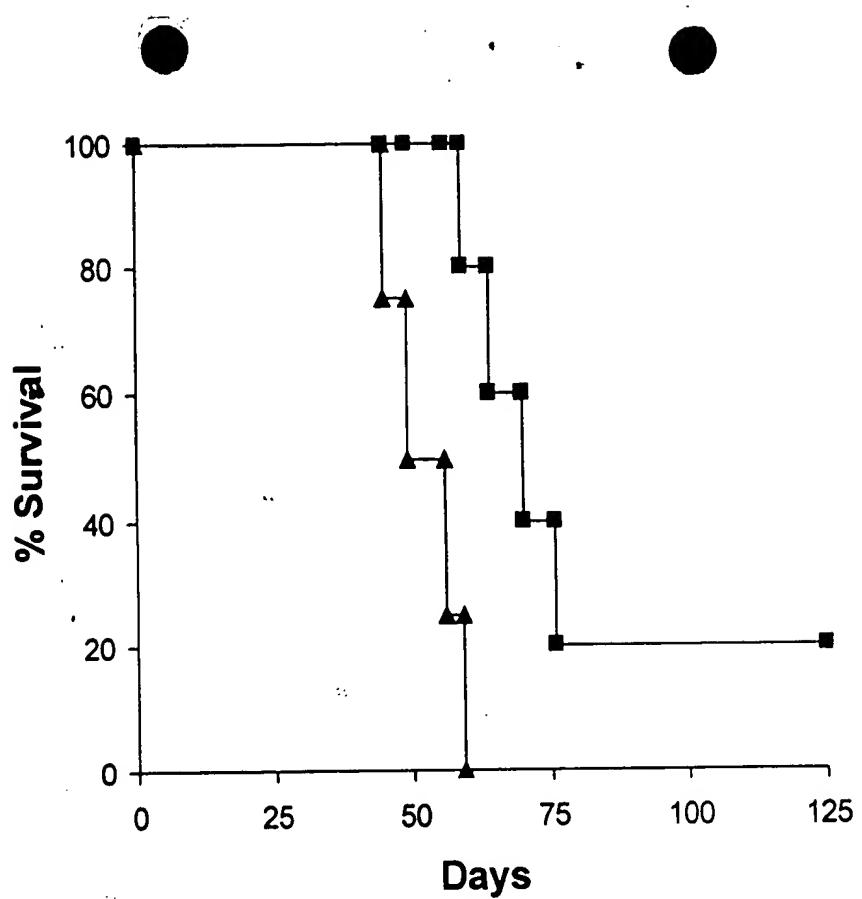


Figure 68

A)



B)

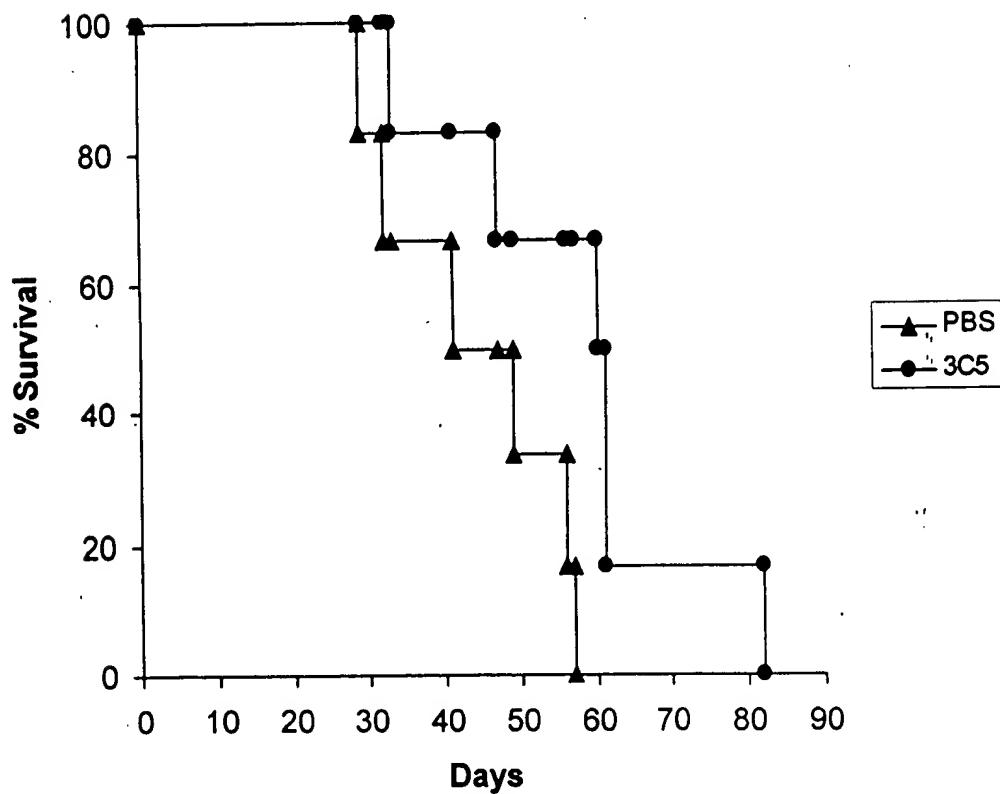


Figure 69

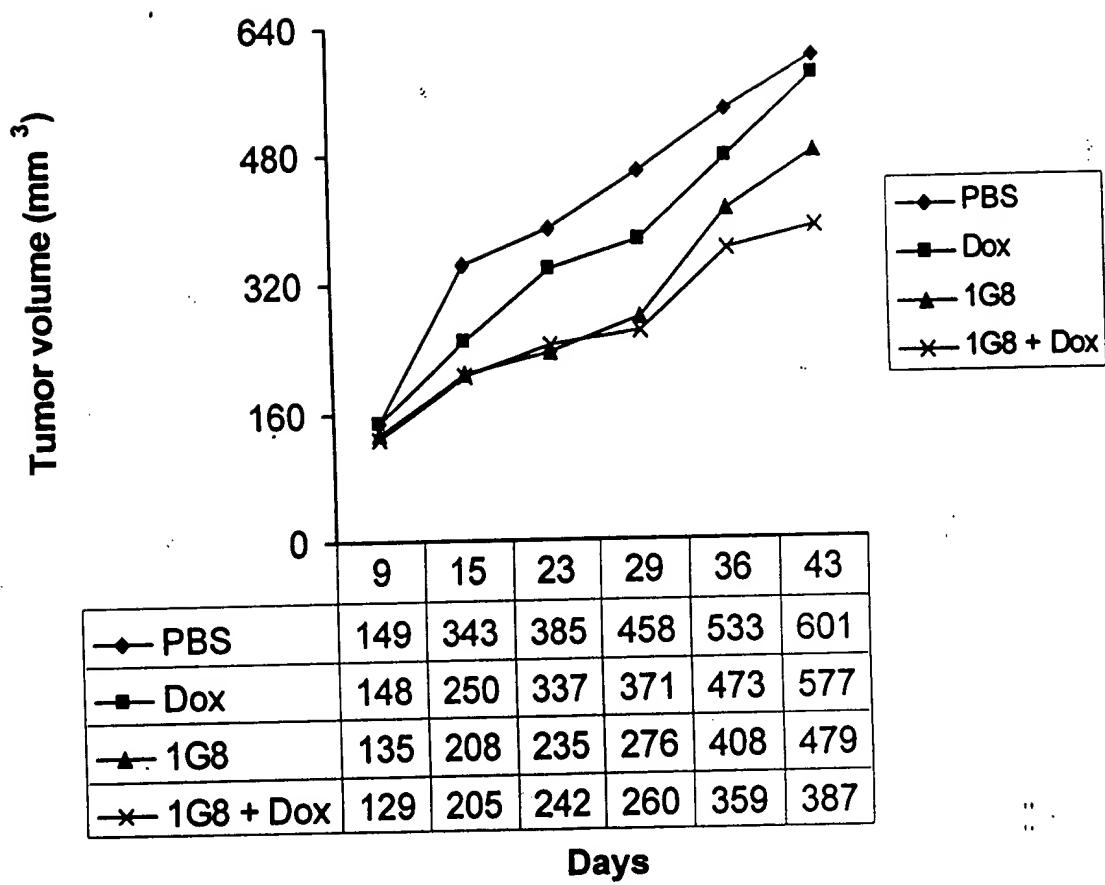


Figure 70

2

Example 18:

PSCA monoclonal antibody mediated inhibition of prostate tumors in vivo

- 5 The following examples demonstrate that unconjugated PSCA monoclonal antibodies inhibit the growth of human prostate tumor xenografts grown in SCID mice, both when administered alone or in combination.

A. Tumor inhibition using multiple unconjugated PSCA mAbs – Study 1

10

MATERIALS AND METHODS

Anti-PSCA Monoclonal Antibodies:

- 15 Murine monoclonal antibodies were raised against a GST-PSCA fusion protein comprising PSCA amino acid residues 18-98 of the PSCA amino acid sequence (FIG. 1B) and expressed in *E. coli*, utilizing standard monoclonal antibody production methods. The following seven anti-PSCA monoclonal antibodies, produced by the corresponding hybridoma cell lines deposited with the American Type Culture Collection on December
20 11, 1998, were utilized in this study:

	<u>Antibody</u>	<u>Isotype</u>	<u>ATCC No.</u>
	1G8	IgG1	HB-12612
	2H9	IgG1	HB-12614
25	2A2	IgG2a	HB-12613
	3C5	IgG2a	HB-12616
	3G3	IgG2a	HB-12615
	4A10	IgG2a	HB-12617
	3E6	IgG3	HB-12618

30

Antibodies were characterized by ELISA, Western blot, FACS and immunoprecipitation for their capacity to bind PSCA. FIG. 49 shows epitope mapping data for the above seven anti-PSCA mAbs as determined by ELISA and Western analysis, as described in the accompanying figure legend, demonstrating that the seven antibodies recognize different epitopes on the PSCA protein. Immunohistochemical analysis of prostate cancer tissues and cells with these antibodies is described in Examples 5 and 6 infra.

5

Antibody Formulation:

- 10 The monoclonal antibodies described above were purified from hybridoma tissue culture supernatants by Protein-G Sepharose chromatography, dialyzed against PBS, and stored at -20°C. Protein determinations were performed by a Bradford assay (Bio-Rad, Hercules, CA).
- 15 A therapeutic antibody cocktail comprising a mixture of the seven individual monoclonal antibodies, as indicated in Table 2, below, was prepared and used for the treatment of SCID mice receiving subcutaneous injections of LAPC-9 prostate tumor xenografts. Mouse IgG, purchased from ICN (Costa Mesa, CA) was used as non-specific control antibody. Prior to injection into mice, all antibodies were sterilized using a 0.22-micron filter.
- 20

TABLE 2: Anti-PSCA Antibody Cocktail

Monoclonal Antibody	Isotype	Amount (% of total)
1G8	IgG1	2.0 mg (16.7%)
2H9	IgG1	1.0 mg (8.3%)
2A2	IgG2a	2.5 mg (20.8%)
3C5	IgG2a	2.0 mg (16.7%)
3G3	IgG2a	2.5 mg (20.8%)
4A10	IgG2a	1.5 mg (12.5%)
3E6	IgG3	0.5 mg (4.2%)

25

Introduction of Prostate Cancer Xenografts into SCID Mice:

The human prostate cancer xenograft line LAPC-9, which expresses very high levels of PSCA, was used to produce tumors in SCID mice (PCT Application No. WO98/16628,
5 supra; Klein et al., 1987, supra).

For injection into IcR-SCID mice (Taconic Farms, Germantown, NY), a single-cell suspension of LAPC-9 was prepared as follows. An LAPC-9 xenograft tumor of approximately 2.0 g in size was harvested from a SCID mouse, minced into very small
10 pieces using scissors and forceps, washed once in RPMI, and digested in a 1% solution of pronase for 20 minutes. After digestion, the cell suspension was washed twice in RPMI, and resuspended in 10 ml of PrEGM medium (Clonetics, Walkersville, MD). After overnight incubation, the cells were harvested and washed once in PrEGM, then passed through a 200-micron nylon filter to remove large clumps and debris. Cells passing
15 through the filter were collected, centrifuged, and resuspended in PrEGM medium. Cells were then counted, and the appropriate number of cells was transferred to a new tube, centrifuged, and resuspended at 2X concentration in RPMI. An equal volume of ice cold Matrigel was then added to the cell suspension, and the suspension was kept on ice prior to injection. For injection, male IcR-SCID mice were shaved on their flanks, and each
20 mouse received a single subcutaneous (s.c.) injection of 1×10^6 cells in a volume of 100 μ l on the right flank. Mice injected with tumor cells were treated with either control antibodies or the anti-PSCA monoclonal antibody preparation as described below.

Treatment Protocol:

25 Twenty SCID mice injected with tumor cells were treated with either control antibodies (mouse IgG) or the anti-PSCA monoclonal antibody cocktail (above) as follows. Ten mice were treated with mouse IgG control antibody and ten mice were treated with the anti-PSCA monoclonal antibody preparation. Injections of 200 μ g of the mouse IgG
30 control antibody or the anti-PSCA monoclonal antibody cocktail were administered intraperitoneally on days -1, +3, +7, +11, +14, and +21 relative to the injection of the

tumor cells. Growth of LAPC-9 tumors was followed by caliper measurements to determine tumor volumes on days +32, +35, +39, +42, +47, +54 and +61 relative to injection of tumor cells. In addition, mice were periodically bled for assaying circulating PSA levels using a commercially available PSA test (American Qualex, San Clemente, CA).

One of the mice in the control group (mouse #2) expired during the course of the study and had no detectable tumor at the time.

10 RESULTS

SCID mice receiving a subcutaneous injection of the LAPC-9 prostate cancer xenograft were treated with either the anti-PSCA mAb preparation or mouse IgG control antibody, as described above. Palpable tumors first appeared in the mouse IgG control group at 4 weeks after tumor cell injection. Tumor volume measurements were initiated on day +32.

The results, which are tabulated in Table 3, below, as well as presented graphically in FIG. 48, show that all of the control mAb-treated mice developed tumors (9 out of 9 surviving, mouse #1, #3-10), but that none of the anti-PSCA mAb treated mice developed any detectable tumor growth (0 out of 10, mouse #11-20). The control-treated animals developed significant tumors rapidly in most instances, and these mice experienced constant tumor growth leading to progressively larger tumor sizes with time. By day 54, all control-treated mice had developed detectable tumors. In sharp contrast to the control-treated group, none of the ten mice treated with the anti-PSCA mAb preparation developed detectable tumors, even after 61 days post xenograft injection.

TABLE 3: Recorded tumor volume (mm³) measurements

MOUSE #*	DAYS						
	32	35	39	42	47	54	61
1 ..	416°	576	578	720	810	1045	1080
2 ..	0	0	0	0			
3 ..	100	269.5	450	476	544	648	810
4 ..	0	0	0	0	0	87.5	151.3
5 ..	338	420	800	900	1087	1265	2002
6 ..	216	250.3	504	476	612	850.5	1050
7 ..	252	472.5	637.5	720	720	720	1306
8 ..	336	532	560	693	1080	1365	1617
9 ..	0	160.9	225	294	478	640	900
10 ..	0	0	195	294	341	504	769.5
11 ..	0	0	0	0	0	0	0
12 ..	0	0	0	0	0	0	0
13 ..	0	0	0	0	0	0	0
14 ..	0	0	0	0	0	0	0
15 ..	0	0	0	0	0	0	0
16 ..	0	0	0	0	0	0	0
17 ..	0	0	0	0	0	0	0
18 ..	0	0	0	0	0	0	0
19 ..	0	0	0	0	0	0	0
20 ..	0	0	0	0	0	0	0

* Mice # 1-10 represent the group treated with the mouse IgG control antibody. Mice # 11-20 represents the group treated with the anti-PSCA mAb cocktail.

5

* Tumor volume corresponds to length (L) x width (W) x height (H) measurements in mm. To determine the ellipsoid volume represented in Figure 1, which accurately represents tumor mass (Tomayko and Reynolds, 1989), we used the formula L x W x H x 1/2.

10

Clinically, the control treated mice all displayed visual symptoms of progressively poor health as tumors developed and expanded. In contrast, the mice in the anti-PSCA mAb treatment group remained active, vigorous, and generally healthy in appearance 15 throughout the treatment period, suggesting no apparent toxicity or obvious side-effects were associated with the treatment.

In addition to tumor volume, mice were bled for determination of circulating PSA. Circulating PSA levels correlated with increasing tumor volumes in the control group, whereas no detectable PSA was observed in the anti-PSCA mAb treated group throughout the experiment.

5

B. Tumor inhibition using multiple unconjugated PSCA mAbs - Study 2

To verify the results described in Example 18, supra, a newly prepared anti-PSCA mAb cocktail was evaluated for growth inhibition of LAPC-9 tumor xenografts *in vivo*, essentially as described above. Briefly, a new batch of each mAb was prepared and mixed together according to the proportions presented in Table 4. All antibodies were tested for PSCA reactivity. SCID mice received a subcutaneous injection of LAPC-9 xenograft cells as described above. The mice were treated with either a cocktail of anti-PSCA mAb, or control preparations of mouse IgG or purified bovine IgG. A bovine IgG control group was included in this study in order to study the effect of bovine IgG copurified with the anti-PSCA antibodies on protein G-sepharose. Two hundred micrograms of antibody was administered to each mouse by intraperitoneal injection on days -1, +3, +7, +11, +14, and +21 relative to the injection of the tumor cells. Tumor volume corresponding to length (L) x (W) x (H) in mm was monitored by caliper measurements, and serum was collected at weekly intervals. To determine the ellipsoid volume of the tumors, which accurately represents tumor mass, we used the formula L x W x H x 1/2 (Tomayko and Reynolds, 1989).

25

TABLE 4: Anti-PSCA antibody cocktail 2

Monoclonal Antibody	Isotype	Amount (% of total)
1G8	IgG1	8.0 mg (16.7%)
2H9	IgG1	4.0 mg (8.3%)
2A2	IgG2a	10.0 mg (20.8%)
3C5	IgG2a	8.0 mg (16.7%)
3G3*	IgG2a	10.0 mg (20.8%)
4A10	IgG2a	6.0 mg (12.5%)
3E6	IgG3	2.0 mg (4.2%)

* One of the monoclonal antibody preparations used to formulate this cocktail, 3G3, demonstrated weak reactivity.

The results of this study are presented in FIG. 53 and confirm the results generated from
5 the study described in Example 18-A, supra. Animals in the anti-PSCA treated group
experienced significant inhibition of tumor cell growth compared with both of the control
groups. No detectable difference in tumor growth was observed in mice that received
either bovine IgG or murine IgG. The tumors in the control groups grew at equal rates
and with similar latency. In contrast, LAPC-9 tumors in mice receiving the anti-PSCA
10 antibody cocktail exhibited a longer latency, a significantly slower rate of growth and
smaller sizes at the end of the experiment. The average tumor volume at the final time
point was 1,139 mm³ for mice treated with murine IgG (day 46), 1091 mm³ for mice
treated with bovine IgG (day 42) and 391 mm³ for anti-PSCA treated mice (day 46). Due
to the large tumor sizes in the bovine IgG treated group, these mice were sacrificed
15 earlier than mice in the other groups. In addition, tumor volume correlated with PSA
levels in the serum of the treated mice. Some mice receiving anti-PSCA antibodies
showed very small tumors or no tumor growth at all, as was previously observed in the
study described in Example 1, supra. No apparent toxicity was associated with
administration of any of this antibody cocktail preparation, consistent with the study
20 described in Example 18-A.

C. Tumor inhibition *in vivo* using single unconjugated PSCA mAbs

Materials and Methods:

25

Several of the monoclonal antibodies described herein were studied for their
ability to inhibit the growth of prostate tumor xenografts in their unconjugated
(or, "naked") form using the previously described tumor challenge assay (see
Examples 18-A and 18-B, above). Generally, the studies were conducted as
30 described above, with slight modifications as described in the results sections
presented below for each of the antibodies assayed.

C1: PSCA mAb 1G8

Anti-PSCA monoclonal antibody 1G8 is an IgG1 isotype antibody. The antitumor effect of 1G8 was evaluated using the LAPC-9 xenograft and mouse IgG as a control. The 5 results presented in FIG. 54 demonstrate that treatment of mice with the 1G8 antibody inhibited tumor growth. Specifically, the average tumor volume at the final time point for the control group was 854 mm³ versus an average tumor volume of 335 mm³ for the 1G8 antibody treated group. These results show that the 1G8 monoclonal antibody can inhibit the growth of prostate tumors when used alone. As with the studies described 10 supra, there was no apparent toxicity associated with the treatment of these animals with the 1G8 mAb.

The effect of the 1G8 monoclonal antibody on the growth of prostate cancers generated with PC-3 cells was also determined. PC-3 cells do not express PSCA. As shown in FIG. 65, the 15 1G8 antibody had no effect on the development of PC-3 xenograft tumors, in sharp contrast to its effect on PSCA-expressing LAPC-9 xenografts. These results clearly show that the 1G8 antibody is inhibiting tumor cell growth through the PSCA antigen.

C2: PSCA mAbs 2A2 and 2H9

20 Two anti-PSCA monoclonal antibodies of different isotypes were evaluated simultaneously for prostate tumor growth inhibition in vivo. Anti-PSCA mAbs 2A2 (IgG2a isotype) and 2H9 (IgG1 isotype) were tested for prostate tumor inhibition as described in Example 18-C1, immediately above. The results presented in FIG. 55 demonstrate striking inhibition of tumor cell growth in the anti-PSCA mAb treated 25 groups versus the control groups. Specifically, the average tumor volume at the final time point was 483 mm³ for mice treated with murine IgG (day 42), 49 mm³ for mice treated with the 2A2 mAb (day 42), and 72 mm³ for the mice treated with 2H9 mAb (day 42). More significantly, tumor incidence was 6/6 mice in the mouse IgG control group, 30 versus 2/7 for the 2A2-treated group and 1/7 for the 2H9-treated group. In the 2A2 treated group, the first tumor appeared at day 25 and the second tumor at day 42. In the

2H9 treated group the single tumor present appeared at day 21. In the mouse IgG control group, 4/6 of the mice had developed tumors by day 21. As with the in vivo studies described above, there was no apparent toxicity associated with the treatment of these animals with the 2A2 or 2H9 mAbs.

5

PSA levels in the serum of the treated mice were significantly lower than in control mice, and correlated directly with tumor volume (FIG. 56). At week 6, the mean PSA serum level in the mouse IgG control group was 35 ng/ml, 2 ng/ml in the 2A2 group, and 8 ng/ml in the 2H9 group.

10

This study further supports the conclusion that a single "naked" anti-PSCA monoclonal antibody is sufficient for anti-tumor activity. In addition, these data demonstrate that mAbs recognizing different PSCA epitopes are effective, and that the anti-tumor effect is not dependent upon a single IgG isotype since both IgG1 (1G8, 2H9) and IgG2a (2A2) mAbs inhibited tumor growth.

15

C3: PSCA mAbs exert growth inhibitory effect specifically through PSCA

In order to demonstrate that PSCA mAbs exert tumor growth inhibition specifically through the PSCA protein, a tumor inhibition study with the 1G8 mAb and PC-3 tumor xenografts was conducted. PC-3 cells do not express endogenous PSCA. This study was conducted as described in Section C1 of this Example, above. The results, shown in FIG. 65, show that the PSCA mAb 1G8 had no effect on the growth of PC-3 tumors in mice over a 40 day period. The results are shown, for comparison, together with a parallel study of the effect of 1G8 on LAPC-9 prostate tumor xenografts (Example C1, above).

20

C4: PSCA mAb 3C5 inhibits the growth of established LAPC-9 prostate tumors in vivo

30

In order to determine whether PSCA mAbs could effect growth of established tumors, the following study was conducted. Briefly, a cohort of SCID mice were injected with 10^6

LAPC-9 cells SQ, essentially as described in examples C1 and C2. After tumors reached a size of approximately 100 cubic millimeters, mice were segregated into two groups, a control group receiving mouse IgG and a treatment group receiving PSCA mAb 3C5. Each mouse was injected IP with control IgG or 3C5 mAb according to the following protocol: 1 mg per injection, three times per week for the first 2 weeks, followed by two times per week in the third week. Tumor volume and PSA measurements were determined as above. The results, shown in FIG. 57, indicate that the 3C5 mAb inhibits the growth of established LAPC-9 prostate tumors *in vivo*. In at least some of the treatment group mice, tumor regression up to 50% of the initial, pre-treatment size of the tumor was observed.

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Bib Data Sheet

SERIAL NUMBER 09/038,261	FILING DATE 03/10/1998 RULE -	CLASS 536	GROUP ART UNIT 1642	ATTORNEY DOCKET NO. 30435.54USU1
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APPLICANTS

ROBERT E. REITER, LOS ANGELES, CA ;
 OWEN N. WITTE, SHERMAN OAKS, CA ;

**** CONTINUING DATA *******

THIS APPLN CLAIMS BENEFIT OF 60/071,141 01/12/1998
 WHICH CLAIMS BENEFIT OF 60/074,675 02/13/1998

**** FOREIGN APPLICATIONS *******

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** SMALL ENTITY **

Foreign Priority claimed	<input type="checkbox"/> yes <input type="checkbox"/> no	STATE OR COUNTRY CA	SHEETS DRAWING 16	TOTAL CLAIMS 45	INDEPENDENT CLAIMS 5
35 USC 119 (a-d) conditions met	<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> Met after Allowance				
Verified and Acknowledged	Examiner's Signature _____ Initials _____				

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TITLE

PSCA: PROSTATE STEM CELL ANTIGEN

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
09/038,261	03/10/1998	ROBERT E. REITER	30435.54USU1

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RESPONSE TO REQUEST CORRECTED FILING RECEIPT**Claims, Fees, Inventors and Continuity**

In response to your request for a corrected Filing Receipt, the Office is unable to comply with your request because:

- The total number of claims appearing on the Filing Receipt does not include multiple dependent claims. The total fee appearing on the Filing Receipt includes the cost of multiple dependent claims that were present at the time the application was filed.
- The filing fee is correct. It includes the surcharge under 37 CFR 1.16(e) for filing an oath/declaration or basic filing fee after the application filing date.
- The inventor information may be truncated if the family name consists of more than 50 characters (letters and spaces combined) and if the given name consists of more than 50 characters (letters and spaces combined). The inventor's residence allows for up to 40 characters (letters and spaces combined).
- The docket number allows a maximum of 25 characters.
- Continuity claimed under 35 USC 120 cannot be added to the Filing Receipt without supplying the relationship (i.e. continuation, divisional...).
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Initial Patent Examination Division (703) 308-1202

PART 2 - COPY TO BE RETURNED WITH RESPONSE



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RECEIPT
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Applicant: R. Reiter and O. Witte Examiner: Dr. Larry Helms
Serial No.: 09/038,261 Group Art Unit: 1643
Filed: March 10, 1998 Docket: 30435.54USU1
Title: PSCA: PROSTATE STEM CELL ANTIGEN AND USES THEREOF

CERTIFICATE UNDER 37 CFR 1.8

I hereby certify that this paper or fee is being deposited with the United States Postal as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on August 15, 2000.

By: *[Signature]*

Name: Richelle Ann Domingo

35 N. Arroyo Parkway, Suite 60
Pasadena, California 91103
August 15, 2000

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

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35 No. Arroyo Parkway, Suite 60
Pasadena, California 91103
(626)395-7801

By: *Sarah B. Adriano*
Name: Sarah B. Adriano
Reg. No.: 34,470
Initials: SBA



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Applicant: R. Reiter and O. Witte
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Filed: March 10, 1998
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By:

Name: Richelle Ann Domingo

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August 15, 2000

Assistant Commissioner for Patents
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35 No. Arroyo Parkway, Suite 60
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By: Sarah B. Adriano
Name: Sarah B. Adriano
Reg. No.: 34,470
Initials: SBA



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: R. Reiter and O. Witte **Examiner:** Dr. Larry Helms
Serial No.: 09/038,261 **Group Art Unit:** 1643
Filed: March 10, 1998 **Docket No.:** 30435.54USU1
Title: PSCA: PROSTATE STEM CELL ANTIGEN AND USES THEREOF

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Richelle Ann Domingo

REQUEST FOR CORRECTED FILING RECEIPT

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Dear Sir:

Enclosed is a photocopy of the filing receipt from the United States Patent and Trademark Office in the above-identified application showing requested corrections. Correction was previously requested, filed herewith as Exhibit 1, and have not made by the Patent Office.

Once again, applicants point out that the filing receipt is erroneous in the following respects as reflected in the papers originally filed:

Applicant(s) Robert E. Rieter, Los Angeles, CA; Owen N. Witte, Sherman Oaks, CA.

Continuing Data as Claimed by Applicants – Provisional Application No. 60/071,141 01/12/98.

The corrected filing receipt should read:

Applicant(s) Robert E. Reiter, Los Angeles, CA; Owen N. Witte, Sherman Oaks, CA.

Continuing Data as Claimed by Applicant –

Provisional Application Nos. 60/071,141 01/12/98

60,074,675 02/13/98

08/814,279 03/10/97.

Robert Reiter and Owen V. Cole
Serial No.: 09/038,261
Filed: March 10, 1998
Page 2

A copy of the Change of Correspondence Address is also included as Exhibit 2. A copy of the Filing Receipt to be corrected is also included as Exhibit 3.

Correction of the records of the United States Patent and Trademark Office and issuance of a corrected filing receipt are respectfully requested.

No fee is deemed necessary in connection with the filing of this Request for Corrected Filing Receipt. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-0306.

Respectfully submitted,

Sarah B. Adriano

Sarah B. Adriano
Attorney for Applicants
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35 No. Arroyo Parkway, Suite 60
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626/395-7801

Exhibit J

COPY

Receipt is hereby acknowledged for the following in the U.S. Patent and Trademark Office:

Applicant: Robert E. Reiter and Owen N. Witte
Serial No: 09/038,261
Filed: March 10, 1998
Title: PSCA: PROSTATE STEM CELL ANTIGEN

Docket: 30435.54USU1
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Serial No: 09/038,261
Filed: March 10, 1998
Title: PSCA: PROSTATE STEM CELL ANTIGEN

Docket: 30435.54USU1
Date of Mailing: July 10, 1998

Transmittal sheet, in duplicate, containing Certificate under 37 CFR 1.8.
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Patent

SBA





IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

COPY

Applicant: Robert E. Reiter and Owen N. Witte
Serial No.: 09/038,261
Filed: March 10, 1998
Docket: 30435.54USU1
Title: PSCA: PROSTATE STEM CELL ANTIGEN

CERTIFICATE UNDER 37 CFR 1.8

I hereby certify that this paper or fee is being deposited with the United States Postal as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on July 10, 1998.

By: Renato Marco P. Domingo
Name: Renato Marco P. Domingo

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

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MANDEL & ADRIANO
725 Main Street
Half Moon Bay, CA 94019
(213)258-5580

By: Sarah B. Adriano
Name: Sarah B. Adriano
Reg. No.: 34,470
Initials: SBA



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

COPY

Applicant: Robert E. Reiter and Owen N. Witte
Serial No.: 09/038,261
Filed: March 10, 1998
Docket: 30435.54USU1
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MANDEL & ADRIANO
725 Main Street
Half Moon Bay, CA 94019
(213)258-5580

By: Sarah B. Adriano
Name: Sarah B. Adriano
Reg. No.: 34,470
Initials: SBA



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Robert E. Reiter, et al.	Examiner:	Not yet known
Serial No.:	09/038,261	Group Art Unit:	1643
Filed:	March 10, 1998	Docket No.:	30435.54USU1
Title:	PSCA: PROSTATE STEM CELL ANTIGEN		

CERTIFICATE UNDER 37 CFR 1.8:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on July 10, 1998.


Renato Marco P. Domingo

REQUEST FOR CORRECTED FILING RECEIPT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Enclosed is a photocopy of the filing receipt from the United States Patent and Trademark Office in the above-identified application showing requested corrections. The filing receipt is erroneous in the following respects as reflected in the papers originally filed:

Applicant(s) Robert Rieter; Owen Witte.

Continuing Data as Claimed By Applicant- Provisional Application No. 60/071,141 01/12/98

Robert A. Figlin, et al.
Serial No.: 60/080,512
Filed: April 2, 1998
Page 2

COPY

The correction should read: Applicant(s) Robert Reiter, Los Angeles, CA; Owen Witte, Sherman Oaks, CA.

Continuing Data as Claimed By Applicant- U.S. Serial No. 08/814,279 03/10/97

U.S. Serial No. 60/071,141 01/12/98

U.S. Serial No. 60/074,675 02/13/98

Correction of the records of the United States Patent and Trademark Office and issuance of a corrected filing receipt are respectfully solicited.

No fee is deemed necessary in connection with the filing of this Request for Corrected Filing Receipt. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-0306.

Respectfully submitted,

Sarah B. Adriano
Sarah B. Adriano
Attorney for Applicants
Mandel & Adriano
725 Main Street
Half Moon Bay, California 94019
213/ 258-5580

Exhibit Q

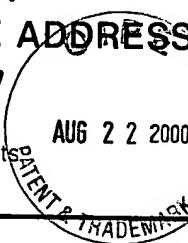
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PTO/SB/122 (11-96)

Approved for use through 6/30/99. OMB 0651-0035
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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**CHANGE OF
CORRESPONDENCE ADDRESS**
Application

 Address to:
 Assistant Commissioner for Patents
 Washington, D.C. 20231


Application Number	09/038,261
Filing Date	March 10, 1998
First Named Inventor	Reiter, Robert E.
Group Art Unit	1642
Examiner Name	Worrall, T.
Attorney Docket Number	30435.54USU1

Please change the Correspondence Address for the above-identified application to:

 Customer Number

Type Customer Number here

 Place Customer
Number Bar Code
Label here

OR

<input type="checkbox"/> Firm or Individual Name	MANDEL & ADRIANO			
Address	35 N Arroyo Parkway, Suite 60			
Address				
City	Pasadena	State	CA	ZIP 91103
Country	United States of America			
Telephone	(626) 395-7801	Fax	(626) 395-0694	

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I am the :

 Applicant.

 Assignee of record of the entire interest.
Certificate under 37 CFR 3.73(b) is enclosed.

 Attorney or agent of record .

Typed or Printed Name	Sarah B. Adriano Reg. No. 34,470
Signature	
Date	August 6, 1999

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

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Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
09/038,261	03/10/98	1642	\$952.00	30435.54USU1	16	45	5

MANDEL AND ADRIANO
SARAH B ANRIANO
725 MAIN STREET
HALF MOON BAY CA 94019

MANDEL AND ADRIANO
35 NO. ARROYO PARKWAY, STE 60
PASADENA, CA 91103

Receipt is acknowledged of this patent application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Application Processing Division's Customer Correction Branch within 10 days of receipt. Please provide a copy of the Filing Receipt with the changes noted thereon.

Applicant(s) ROBERT E. RIETER, LOS ANGELES, CA; OWEN N. WITTE,
SHERMAN OAKS, CA. REITER

CONTINUING DATA AS CLAIMED BY APPLICANT
PROVISIONAL APPLICATION NO. 60/071,141 01/12/98

FOREIGN FILING LICENSE GRANTED 04/01/98
TITLE
PSCA: PROSTATE STEM CELL ANTIGEN

PRELIMINARY CLASS: 536

* SMALL ENTITY *

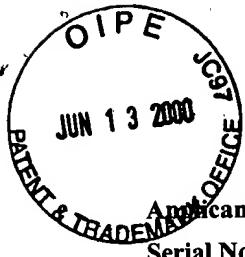
Please add the following:

60/074,675 02/13/98

08/814, 279 03/10/97

DATA ENTRY BY: WILSON, PAMELLA

TEAM: 12 DATE: 12/27/98



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Robert E. Reiter et al.
Serial No.: 09/038,261
Filed: March 10, 1998
Docket: 30435.54USU1
Title: PSCA: PROSTATE STEM CELL ANTIGEN

CERTIFICATE UNDER 37 CFR 1.8

I hereby certify that this paper or fee is being deposited with the United States Postal as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on June 7, 2000.

By:

Name: Renato Marco P. Domingo

35 N. Arroyo Parkway, Suite 60
Pasadena, California 91103
June 7, 2000

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

We are transmitting herewith the attached:

- Transmittal sheet, in duplicate, containing Certificate under 37 CFR 1.8.
- Supplemental Amendment
 - No Additional fee is required
 - The fee has been calculated as shown below in the "Claims as Amended" table
- Exhibits 1-2
- Return postcard

CLAIMS AS AMENDED

Claims Remaining After Amendment	Highest Number Previously Paid For	Present Extra	Rate	Fee
Total Claims	5	= 0	x .00	= \$0.00
Independent Claims	2	= 0	x .00	= \$0.00
MULTIPLE DEPENDENT CLAIM FEE				\$0.00
TOTAL FILING FEE				

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M A N D E L & A D R I A N O
35 No. Arroyo Parkway, Suite 60
Pasadena, California 91103
(626)395-7801

By: Sarah B. Adriano

Name: Sarah B. Adriano
Reg. No.: 34,470
Initials: SBA



GAU1643

Dkt. 30435.54USU1/SBA/TYL/RDG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Robert Reiter and Owen Witte
Serial No. : 09/038,261 Examiner: Dr. Larry Helms
Filed : March 10, 1998 Group Art Unit: 1643
For : PSCA: PROSTATE STEM CELL ANTIGEN AND USES
THEREOF

7/15/00
T.Bray
#14

35 N. Arroyo Pkwy.
Pasadena, California 91103
June 7, 2000

Honorable Assistant Commissioner for Patents
Washington, D.C. 20231

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SUPPLEMENTAL AMENDMENT

Applicants provide herein a supplemental amendment to the amendment submitted in response to the Office Action dated December 6, 1999 issued by the U. S. Patent and Trademark Office in connection with the above-identified application. This supplemental amendment is being submitted with additional documents that were not submitted with the amendment submitted June 6, 2000.

Applicants: Robert Reiter and Owen Witte
U. S. Serial No.: 09/038,261
Filed: March 10, 1998
Page: 2

Applicants are hereby providing the post-filing confirmatory support of applicant's assertion that the methods for inhibiting the growth of prostate tumor cells expressing PSCA, work as claimed in claims 44-48.

Applicants previously provided the brief descriptions of Figures 48, 53, 54, 55, 57, and 65-70 in the amendment dated June 6, 2000. Applicants provide the corresponding Figures as Exhibit 1 herein.

Applicants previously provided a brief description of Figure 48, which describes data from Example 18-A. Applicants provide the text of Example 18 as Exhibit 2 herein.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

No fee is deemed necessary in connection with the filing of this supplemental amendment. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 50-0306.

Respectfully submitted,



Sarah B. Adriano
Registration No. 34,470
SaraLynn Mandel
Registration No. 31,853
Attorneys for Applicants
Mandel & Adriano
35 N. Arroyo Parkway
Pasadena, California 91103
(626) 395-7801

L. Helms

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8 <130> FILE REFERENCE: 30435.54USU1
10 <140> CURRENT APPLICATION NUMBER: 09/038,261A
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323 <223> OTHER INFORMATION: Description of Artificial Sequence: RT-PCR PRIMER
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333 <220> FEATURE:
334 <223> OTHER INFORMATION: Description of Artificial Sequence: RT-PCR PRIMER
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VERIFICATION SUMMARY DATE: 08/09/2000
PATENT APPLICATION: US/09/038,261A TIME: 13:18:16

Input Set : A:\Reiterul.app
Output Set: N:\CRF3\08092000\I038261A.raw

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L:98 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:1
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